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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/773,440	FRADET ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *30-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The Election filed 5/3/06 in response to the Office Action of 2/30/06 is acknowledged and has been entered. Applicant elected group I, PSA, transcriptional mediated amplification assay (TMA), chemiluminescence, and urine with traverse.

The traversal is on the ground(s) that the restriction requirement places an undue burden on Applicant to obtain a reasonable scope of patent protection for the invention. Applicant argues that the USPTO has recognized this burden and has implemented a policy that entitles Applicant to have at least ten sequences searched in the instant application. Applicant further argues that searching all six nucleotides in claim 2 together would not present a "serious burden" on the examiner. Applicant further argues that searching the species of the present invention does not create a "serious burden". Applicant asserts that a search using a PCA3 sequences and generically a second prostate specific nucleic acid should identify potentially relevant art without "serious burden". Applicant further argues that the claimed second prostate specific nucleic acid sequences share similar functionalities "(e.g., they are expressed in the prostate)" and can thus be used to validate, confirm or improve the determination of prostate cancer presence or predisposition in accordance with the present invention. This is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in the Office Action. The species of amplification methods and detection methods represent materially distinct methods which differ at least in method steps, reagents, and criteria for success. The species of samples

represent separate and distinct compounds with different functions such that one species could not be interchanged with the other. The species of "second specific prostate nucleic acids" represent separate and distinct molecules with different structures and functions such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues. Further, Applicants further point-out that MPEP 803.04 states that a reasonable number of nucleotide sequences, normally ten independent and distinct nucleotide sequences, can be examined in a single application without restriction. MPEP 803.04 states that polynucleotide molecules defined by their nucleic acid sequences constitute independent and distinct inventions and the examiner is permitted to allow a reasonable number of sequences in a single application, which the MPEP suggests may be ten sequences. However, MPEP 803.04 does not state that ten independent and distinct nucleotide sequences are required to be examined in a single application without restriction. Since this rule was written, the size of the sequence databases has grown exponentially. Currently, there are approximately eight different databases that accompany the results of a search of one discrete amino acid or nucleotide sequence and each result set from a particular database must be carefully considered. Hence, the search of multiple different polypeptides, and different polypeptide segments in the databases would require an unreasonable amount of searching and review. Hence, the search of every polypeptide recited in claim 2, along with the 8 other sequences that are included in the elected in invention, would require extensive searching and review. Furthermore, it is noted that the literature search,

particularly relevant in this art, is not coextensive and is very important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Note: The following "biological samples" have been rejoined: blood and prostate biopsy.

Claims 1-40 are pending.

Claims 30-36 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 1-29 and 37-40 are currently under consideration.

Objections

Claim 1 is objected to for reciting: "A method for determining a predisposition, or presence of prostate cancer...". There appears to be a word missing after "predisposition". It appears Applicant may intend the claim to recite: "A method for determining a predisposition for, or presence of prostate cancer...". Proper correction is required.

Claims 10, 29, and 39 are objected to for reciting the term "chimiluminescence". This appears to be a typographical error. It is suspected Applicant intended the claims

to recite the term "chemiluminescence", as written in the reply to the restriction requirement, rather than "chimiluminescence. Proper correction is required.

Claims 9 and 14 are objected to for reciting "...a primer pair composed of SEQ ID NO...". A primer pair is "comprised" of two *distinct* polynucleotides and is not "composed" of two SEQ ID NOs. Thus, it appears Applicant intended to claim "....a primer pair comprised of a polynucleotide consisting of the sequence set forth in SEQ ID NO:3 and a polynucleotide consisting of the sequence set forth in SEQ ID NO:4" and "....a primer pair comprised of a polynucleotide consisting of the sequence set forth in SEQ ID NO:1 and a polynucleotide consisting of the sequence set forth in SEQ ID NO:2".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-29 and 37-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and dependant claims 2-29, 38, and 40 are rejected because claims 1 is indefinite for reciting: "a predetermined cut off value". The specification indicates that a value above "a predetermined cut off value" is indicative of the presence or

predisposition to develop prostate cancer (paragraph 91, in particular). However, the specification and the claims do not distinctly claim what is meant by a predetermined cut off value. It is unclear exactly to what the "predetermined cut off value" refers. It is unclear how the exact numeric value of the "predetermined cut off value" will be determined.

Claim 1 and dependant claims 2-29, 38, and 40 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. Claim 1 recites a method for determining a predisposition for or presence of prostate cancer comprising detecting oligonucleotide probes that hybridize to PCA3 polynucleotides; however, it is unclear what kind of result would be indicative of a predisposition for or presence of prostate cancer. Thus, there is a missing step involving *correlating* a detected amount to a predisposition for or presence of prostate cancer. See MPEP § 2172.01.

Claim 1 and dependant claims 2-29, 38, and 40 are rejected as indefinite because claim 1 recites a polynucleotide sequence that hybridizes under "*high* stringency conditions", as the specification does not distinctly define the limitations of such conditions. For example, the specification teaches that exemplary high stringent conditions are hybridization in 6 X SSC or 5 X SSPE, 5 X Denhardt's solution, 0.5% SDS, and 100mg/ml denatured salmon sperm DNA at degrees Celsius; and washing in 2 X SSC with 0.1% SDS, and at 65 degrees Celsius (paragraph 45). However, those

conditions are not *defined* by the claims and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. This rejection can be obviated by *distinctly* defining the conditions, *including washing conditions*, under which high stringent conditions are practiced.

Claim 1 and dependent claims 2-29, 38, and 40 are rejected because claim 1 recites: "...i) a polynucleotides according to SEQ ID NOs 9, 10 and 13". It is unclear whether the claims are drawn to a single polynucleotide ("a") or multiple polynucleotides. Further, it is unclear what Applicant means by "according to". It is suspected that Applicant is intending to claim "...i) a polynucleotide comprising SEQ ID NO 9, 10, or 13".

Claim 4 is rejected for reciting: "The method of claim 3, wherein said PSA sequence hybridizes to human kallikrein 2". There is insufficient antecedent basis for the term "said PSA sequence". Thus, it is unclear exactly what is hybridizing to human kallikrein 2.

Claim 19 is rejected for reciting: "...said at least one prostate cell". There is insufficient antecedent basis for the term "said at least one prostate cell". Thus, it is unclear exactly what "said at least one prostate cell" means.

Claim 29 is rejected as indefinite for reciting the term "homogenous detection method". The specification and the claims do not distinctly indicate what is meant by a homogenous detection method. Thus, it is unclear exactly what is being claimed.

Claim 37 and dependant claim 38 are rejected as indefinite because claim 37 recites: "...a prostate cancer specific PCA3 sequence". The specification and the claims do not distinctly indicate what is meant by a "PCA3 sequence". It is suspected Applicant intended the claim to recite: "...a prostate cancer specific PCA3 polynucleotide sequence".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 12, 16 and dependent claims 2, 3, 5-11, 13-15, 17-29, 38 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to every oligonucleotide that hybridizes to a PCA3 polynucleotide, every oligonucleotide that hybridizes to a second prostate-specific polynucleotide, every sequence that hybridizes to human kallikrein 2, any molecular

beacon, and every molecular beacon that hybridizes to a PSA amplification product (see claims 1, 4, 12, and 16). This means that the claims are drawn to any and all DNA molecules that hybridize under a wide range of conditions to PCA3, prostate-specific polynucleotides, kallikrein 2, any amplification product, and any amplification product of PSA polynucleotides. Said molecules would include a substantial number of nucleic acids that have a low percent sequence identity to PCA3, a substantial number of nucleic acids that have a low percent sequence identity to prostate-specific polynucleotides, a substantial number of nucleic acids that have a low percent sequence identity to kallikrein 2 nucleic acids, a substantial number of nucleic acids that have a low percent sequence identity to any amplification products, and a substantial number of nucleic acids that have a low percent sequence identity to any amplification products of PSA that would hybridize with low specificity under low to moderate stringency conditions. The specification discloses examples of hybridization conditions. For example, the specification teaches that exemplary high stringent conditions are hybridization in 6 X SSC or 5 X SSPE, 5 X Denhardt's solution, 0.5% SDS, and 100mg/ml denatured salmon sperm DNA at degrees Celsius; and washing in 2 X SSC with 0.1% SDS, and at 65 degrees Celsius (paragraph 45). However, those conditions are not *defined* by the claims and the specification does not disclose a limiting definition of "high stringency".

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial

structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claim are the recitation of SEQ ID NO:3 and 4 as oligonucleotides that hybridize to a PCA3 polynucleotide, SEQ ID NO:1 and 2 as oligonucleotides that hybridize to a second prostate-specific polynucleotide, SEQ ID NO:5 as a PSA molecular beacon, and SEQ ID NO:6 as PCA3 molecular beacon. Accordingly, in the absence of sufficient *recitation* of distinguishing identifying characteristics or conditions of oligonucleotides that hybridize to PCA3 polynucleotides, oligonucleotides that hybridize to a second prostate-specific polynucleotide, sequences that hybridize to human kallikrein 2, or molecular beacons the specification does not provide adequate written description of the claimed genera.

The findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that " [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. At 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not

> specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such

characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. Thus, the instant specification may provide an adequate written description of oligonucleotides that hybridize to PCA3, primer pairs that are specific to PCA3, oligonucleotides that hybridize to a second prostate-specific polynucleotide, primer pairs that are specific for a second prostate-specific polynucleotide, sequences that hybridize to human kallikrein 2, every molecular beacon, and PSA molecular beacons, per Lilly by structurally describing representative hybridization sequences or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe oligonucleotides that hybridize to PCA3, oligonucleotides that hybridize to a second prostate-specific polynucleotide, sequences that hybridize to human kallikrein 2, molecular beacons, or PSA molecular beacons in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses SEQ ID NO:3 and 4 as oligonucleotides that hybridize to a PCA3 polynucleotide, SEQ ID NO:1 and 2 as oligonucleotides that

hybridize to a second prostate-specific polynucleotide, SEQ ID NO:12 as a sequences that hybridize to human kallikrein 2, SEQ ID NO:5 as a PSA molecular beacon, and SEQ ID NO:6 as PCA3 molecular beacon, this does not provide a description of the broadly claimed genera of oligonucleotides that hybridize to a PCA3 polynucleotide, oligonucleotides that hybridize to *any* second prostate-specific polynucleotide, sequences that hybridize to human kallikrein 2, molecular beacons that hybridize to any amplification product, or molecular beacons that hybridize to any amplification products of PSA polynucleotides that would satisfy the standard set out in Enzo because the specification provides no functional characteristics coupled to structural features.

Further, the specification also fails to describe oligonucleotides that hybridize to PCA3, oligonucleotides that hybridize to a second prostate-specific polynucleotide, sequences that hybridize to human kallikrein 2, molecular beacons that hybridize to any amplification product, or molecular beacons that hybridize to every PSA amplification product by the test set out in Lilly because the specification only describes SEQ ID NO:3 and 4 as oligonucleotides that hybridize to a PCA3 polynucleotide, SEQ ID NO:1 and 2 as oligonucleotides that hybridize to a second prostate-specific polynucleotide, SEQ ID NO:12 as a sequences that hybridize to human kallikrein 2, SEQ ID NO:5 as a PSA molecular beacon, and SEQ ID NO:6 as PCA3 molecular beacon. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of oligonucleotides that hybridize to PCA3, oligonucleotides that hybridize to a second prostate-specific polynucleotide, sequences that hybridize to human kallikrein 2,

molecular beacons, molecular beacons that hybridize with any amplification product, or molecular beacons that hybridize to PSA that is required to practice the claimed invention.

Claim 37 and dependent claim 39 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of primer pairs specific to a PCA3 sequence and a genus of primer pairs specific to any prostate specific nucleic acid sequence. However, the written description in this case only sets forth a primer pair specific for PCA3 consisting of a polynucleotide consisting of the sequence set forth in SEQ ID NO:3 and a polynucleotide consisting of the sequence set forth in SEQ ID NO:4 (see claim 9) and a primer pair specific for PSA consisting of a polynucleotide consisting of the sequence set forth in SEQ ID NO:1 and a polynucleotide consisting of the sequence set forth in SEQ ID NO2 (see claim 14). The specification does not disclose any other primer pairs as broadly encompassed in the claims.

The specification teaches how primer pairs *could* be designed and some examples of sequences which they could amplify (paragraph 106, in particular). However, the written description only reasonably conveys a primer pair specific for PCA3 consisting of a polynucleotide consisting of the sequence set forth in SEQ ID

NO:3 and a polynucleotide consisting of the sequence set forth SEQ ID NO:4 (see claim 9) and a primer pair specific for PSA consisting of a polynucleotide consisting of the sequence set forth in SEQ ID NO:1 and a polynucleotide consisting of the sequence set forth SEQ ID NO2 (see claim 14). A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to that genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural features that are common to the genus. That is, the specification provides neither a representative number of primer pairs that encompass the genus of primer pairs specific to a PCA3 sequence and a genus of primer pairs specific to any prostate specific nucleic acid sequence nor does it provide a description of structural features that are common to the genera. Since the disclosure fails to describe common attributes or characteristics that identify members of the genera, and because the genera is highly variant, the disclosure of forth a primer

pair specific for PCA3 consisting of a polynucleotide consisting of the sequence set forth in SEQ ID NO:3 and a polynucleotide consisting of the sequence set forth in SEQ ID NO:4 (see claim 9) and a primer pair specific for PSA consisting of a polynucleotide consisting of the sequence set forth in SEQ ID NO:1 and a polynucleotide consisting of the sequence set forth in SEQ ID NO2 is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genera as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of primer pairs specific to a PCA3 sequence or the genus of primer pairs specific to any prostate specific nucleic acid sequence, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound itself is required. See *Fiers v. Revel*, 25

USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an primer pair specific for PCA3 wherein said primer pair consists of a polynucleotide consisting of the sequence set forth in SEQ ID NO:3 and a polynucleotide consisting of the sequence set forth in SEQ ID NO:4, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. 112, first paragraph. Further, only an primer pair specific for prostate specific nucleic acid sequence wherein said primer pair consists of a polynucleotide consisting of the sequence set forth in SEQ ID NO:1 and a polynucleotide consisting of the sequence set forth in SEQ ID NO:2, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-29, 38 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining a predisposition for and the presence of prostate cancer in a patient comprising contacting polynucleotides from a patient's *urine*, blood, or prostate biopsy sample and

polynucleotides from a corresponding *control urine, blood, or prostate biopsy* sample from a patient that does not have prostate cancer with oligonucleotides that hybridize under *high stringency* to a polynucleotide sequence within SEQ ID NO:9, 10, or 13 and contacting said samples with oligonucleotides that hybridize under *high stringency* to the polynucleotide encoding PSA, detecting the *presence* of a polynucleotide encoding PSA with a molecular beacon comprising SEQ ID NO:5 that binds *with high stringency* to the polynucleotide encoding PSA and detecting the *amount* of polynucleotides comprising SEQ ID NO:9, 10, or 13 with a molecular beacons comprising SEQ ID NO:6 that hybridizes *with high stringency* to amplification products from SEQ ID NO:9, 10, or 13, wherein the detection of polynucleotides encoding PSA and the detection of an elevation in levels of polynucleotides comprising SEQ ID NO:9, 10, or 13 in the patient sample, as compared to the control sample, is indicative of a predisposition for and the presence of prostate cancer, and wherein high stringency hybridization is performed in 6 X SSC or 5 X SSPE, 5 X Denhardt's solution, 0.5% SDS, and 100mg/ml denatured salmon sperm DNA at degrees Celsius; and washing in 2 X SSC with 0.1% SDS, and at 65 degrees Celsius, does not reasonably provide enablement for a method for determining a predisposition for and the presence of prostate cancer in a patient comprising contacting polynucleotides from *any type of biological sample* with *any* oligonucleotides that hybridize to a polynucleotide sequence within SEQ ID NO:9, 10, or 13 or a complementary sequence thereof, contacting said biological sample with *any* oligonucleotide that hybridizes with a second prostate specific polynucleotide, detecting the presence of the second prostate specific polynucleotide with *any* molecular beacon

which binds an amplification product of the second prostate specific polynucleotide and detecting the amount of polynucleotides comprising SEQ ID NO:9, 10, or 13 with *any* molecular beacon which binds an amplification product from SEQ ID NO:9, 10, or 13, and determining the presence or absence of prostate cancer in the biological sample by *any* type of comparison between the amount of detected SEQ ID NO:9, 10, or 13 polynucleotide and *any* predetermined cut off value. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are drawn to a method for determining a predisposition for and the presence of prostate cancer in a patient comprising contacting polynucleotides from *any type of biological sample* with *any* oligonucleotides that hybridize to a polynucleotide sequence within SEQ ID NO:9, 10, or 13 or a complementary sequence thereof, contacting said biological sample with *any* oligonucleotide that hybridizes with a second prostate specific polynucleotide, detecting the presence of the second prostate specific polynucleotide with *any* molecular beacon which binds an amplification product

of the second prostate specific polynucleotide and detecting the amount of polynucleotides comprising SEQ ID NO:9, 10, or 13 with *any* molecular beacon which binds an amplification product from SEQ ID NO:9, 10, or 13, and determining the presence or absence of prostate cancer in the biological sample by *any* type of comparison between the amount of detected SEQ ID NO:9, 10, or 13 polynucleotide and *any* predetermined cut off value.

The specification discloses (pages 34-40, in particular) a method for determining a predisposition for and the presence of prostate cancer in a patient comprising contacting polynucleotides from a patient's *urine, blood, or prostate biopsy* sample and polynucleotides from a corresponding *control urine, blood, or prostate biopsy* sample from a patient that does not have prostate cancer with oligonucleotides that hybridize under *high stringency* to a polynucleotide sequence within SEQ ID NO:9, 10, or 13 and contacting said samples with oligonucleotides that hybridize under *high stringency* to the polynucleotide encoding PSA, detecting the *presence* of a polynucleotide encoding PSA with a molecular beacon the binds *with high stringency* to the polynucleotide encoding PSA and detecting the *amount* of polynucleotides comprising SEQ ID NO:9, 10, or 13 with molecular beacons that hybridize *with high stringency* to amplification products from SEQ ID NO:9, 10, or 13, wherein the detection of polynucleotides encoding PSA and an elevation in levels of polynucleotides comprising SEQ ID NO:9, 10, or 13 in the patient sample, as compared to the control sample, is indicative of a predisposition for and the presence of prostate cancer.

The state of the prior art dictates that if a molecule such as a PCA3 polynucleotide is to be used as a surrogate for a diseased state in conjunction with a marker for PSA polynucleotides, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotides to be used in a diagnostic manner. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated

against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of the polynucleotides' expression including the correlation to a diseased state, one of skill in the art would not be able to predictably use the polynucleotides in any diagnostic setting without undue experimentation. In the instant case, the specification provides guidance regarding how to determine a predisposition for or the presence of prostate cancer by detecting PSA and PCA3 polynucleotides and comparing PSA and PCA3 polynucleotide expression levels to a proper control. However, the broad nature of the claims do not provide enough guidance to indicate *what* to use to predictably detect the polynucleotide markers, what kind of biological sample could be used to perform the method with any degree of predictability of success, or how detected levels would be compared to determine, with any degree of predictability, whether a patient has a predisposition for or has prostate cancer. As indicated in the written description rejection (see above), the claims are broadly drawn to methods using detection polynucleotides that would hybridize with low specificity under low to moderate stringency conditions to PCA3, prostate-specific polynucleotides, kallikrein 2 nucleic acids, amplification products, and amplification products of PSA. The vast majority of said detection polynucleotides would *not* hybridize under *high* stringency conditions to the marker polynucleotides (PCA3, PSA, amplification products of PCA3, and amplification products of PSA). Therefore, the vast majority of the detection polynucleotides encompassed by the claims would not specifically detect the marker genes and, therefore could not detect a predisposition for or the presence of prostate

cancer with any expectation of success. Further, it has not been shown that the claimed method would function with any predictability of success by using just any biological sample since it has not been shown that every biological sample could be used with the claimed method to predictably detect a predisposition for or the presence of prostate cancer. Further, it has not been shown that every type of comparison of the expression levels to every type of value would predictably determine whether a patient has a predisposition for or the presence of prostate cancer.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method for determining a predisposition for and the presence of prostate cancer in a patient comprising contacting polynucleotides from *any type of biological sample* with *any* oligonucleotides that hybridize to a polynucleotide sequence within SEQ ID NO:9, 10, or 13 or a complementary sequence thereof, contacting said biological sample with *any* oligonucleotide that hybridizes with a second prostate specific polynucleotide, detecting the presence of the second prostate specific polynucleotide with *any* molecular beacon which binds an amplification product of the second prostate specific polynucleotide and detecting the amount of polynucleotides comprising SEQ ID NO:9, 10, or 13 with *any* molecular beacon which binds an amplification product from SEQ ID NO:9, 10, or 13, and determining the presence or absence of prostate cancer in the biological sample by *any* type of comparison between the amount of detected SEQ ID NO:9, 10, or 13 polynucleotide and *any* predetermined cut off value, and applicant has not enabled said method because it has not been shown that said method would function with any

predictability of success when using *any type of biological sample* with *any* oligonucleotides that hybridize to a polynucleotide sequence within SEQ ID NO:9, 10, or 13 or a complementary sequence thereof, *any* oligonucleotide that hybridizes with a second prostate specific polynucleotide, *any* molecular beacon which binds an amplification product of the second prostate specific polynucleotide, *any* type of comparison between the amount of detected SEQ ID NO:9, 10, or 13 polynucleotide and *any* value.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Claims 37 and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting prostate cancer in a patient comprising detecting PCA3 polynucleotides and a second prostate specific nucleic acid in a urine sample, does not reasonably provide enablement for a method for detecting prostate cancer in a patient comprising detecting PCA3 polynucleotides and a second prostate specific nucleic acid in any type of biological sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are drawn to a method for detecting prostate cancer in a patient comprising detecting PCA3 polynucleotides and a second prostate specific nucleic acid in *any* type of biological sample.

The specification teaches a method for detecting prostate cancer in a patient comprising detecting PCA3 polynucleotides and a second prostate specific nucleic acid in a urine, blood, or prostate biopsy sample (page 53, in particular).

The state of the prior art dictates that if a molecule such as a PCA3 polynucleotide is to be used as a surrogate for a diseased state in conjunction with a marker for PSA polynucleotides, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotides to be used in a diagnostic manner. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points,

establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of the polynucleotides' expression including the correlation to a diseased state, one of skill in the art would not be able to predictably use the polynucleotides in any diagnostic setting without undue experimentation. In the instant case, the specification provides guidance regarding how to determine a predisposition for or the presence of prostate cancer by detecting PSA and PCA3 polynucleotides and comparing PSA and PCA3 polynucleotide expression levels to a proper control. However, it has not been shown that the claimed method would function with any predictability of success by using just

any biological sample since it has not been shown that every biological sample could be used with the claimed method to predictably detect a predisposition for or the presence of prostate cancer.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method for detecting prostate cancer in a patient comprising detecting PCA3 polynucleotides and a second prostate specific nucleic acid in *any* type of biological sample, and applicant has not enabled said method because it has not been shown that every biological sample could be used with said method to predictably detect prostate cancer.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-8, 10, 18-20, 22, 25, 26, 28, 29, and 37-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Bussemakers et al (US 7,008,765 B1; filed 4/9/98).

Claim 1 is drawn to a method for determining a predisposition for or the presence of prostate cancer in a patient comprising (a) contacting a biological sample of said patient with at least one oligonucleotide that hybridizes to a PCA3 polynucleotide selected from the group consisting of: (i) a polynucleotide according to SEQ ID NOs:9, 10, and 13; (ii) a polynucleotide sequence that hybridizes under high stringency conditions to the polynucleotide sequence in (i); and (iii) a polynucleotide sequence fully complementary to (i) or (ii); and contacting said biological sample with at least one oligonucleotide that hybridizes with a second prostate specific polynucleotide, (b) detecting in said biological sample an amount of PCA3 and second prostate specific polynucleotides; and comparing the amount of PCA3 polynucleotide that hybridizes to the oligonucleotide to a predetermined cut off value, and therefrom determining the presence or absence of prostate cancer in the biological sample. Claims 2 and 3 are drawn to the method of claim 1, wherein said second specific prostate specific nucleic acid is PSA. Claim 4 is drawn to the method of claim 3, wherein said PSA sequence hybridizes to kallikrein 2. Claim 5 is drawn to the method of claim 1 wherein the amount of PCA3 polynucleotide and of the second specific prostate cancer polynucleotide is determined using an assay selected from the group consisting of: (a) an amplification assay and (b) a hybridization assay. Claim 6 is drawn to the method of claim 5 wherein said amplification assay is an in vitro RNA amplification method. Claim 7 is drawn to

the method of claim 6, wherein said RNA amplification method is transcription mediated amplification assay (TMA). Claim 8 is drawn to the method of claim 6, wherein said amplification of PCA3 and said prostate specific nucleic acid is performed simultaneously. Claim 10 is drawn to the method of claim 6, wherein said detection is performed by chemiluminescence. Claim 18 is drawn to the method of claim 1, wherein said sample contains at least one prostate cell and said at least one cell is collected from said sample prior to step (a). Claim 19 is drawn to the method of claim 18 wherein said nucleic acid is extracted from at least one prostate cell. Claim 20 is drawn to the method of claim 19, wherein said nucleic acid is RNA. Claim 20 is drawn to the method of claim 1 wherein said sample is selected from the group consisting of urine, blood or fraction thereof, and prostate biopsy. Claim 25 is drawn to the method of claim 1, further comprising (c) repeating steps (a) and (b) using a biological sample from the patient at a subsequent point in time; and (d) comparing the relative amount of said PCA3 polynucleotide detected in step (c) to the relative amount of PCA3 polynucleotide detected in step (b) and therefrom monitoring the progression of prostate cancer in the patient. Claim 26 is drawn to the method of claim 1, wherein the detection of the second prostate specific polynucleotide validates a negative result for PCA3 detection. Claim 28 is drawn to the method of claim 6, wherein RNA is extracted using a target capture method. Claim 29 is drawn to the method of claim 1, wherein said detection of PCA3 is carried out using chemiluminescent labels in a homogenous detection method. Claim 37 is drawn to a method for detecting prostate cancer in a human patient comprising (a) performing an in vitro nucleic acid amplification assay on a biological

sample of said patient or extract thereof using a first primer pair which is specific to a prostate cancer specific PCA3 sequence and a second primer pair which is specific to a prostate specific nucleic acid sequence; and (b) detection of said PCA3 nucleic acid sequence or a level thereof correlates with a risk of developing prostate cancer or to a presence of prostate cancer in said patient, and wherein an absence of detection of said PCA3 nucleic acid sequence or lower level thereof in said sample validates an absence of prostate cancer or a lower risk of developing same, when said second prostate specific nucleic acid is detected. Claim 38 is drawn to the method of claim 1, wherein said nucleic acid amplification is carried-out in real time. Claim 39 is drawn to the method of claim 37, wherein said detection is performed by chemiluminescence. Claim 40 is drawn to the method of claim 8 wherein said amplification of PCA3 and said second prostate specific nucleic acid is performed simultaneously in one container.

Bussemakers et al teaches a sequence corresponding to PCA3, SEQ ID NO:6, that is 99.5% homologous to instant SEQ ID NO:9 and shares 99.6% local similarity to the first 2036 amino acids of instant SEQ ID NO:9 (see attached sequence comparisons). SEQ ID NO:6 is 100% identical to instant SEQ ID NO:10 (see attached sequence comparisons). SEQ ID NO:6 is 89.1% homologous to instant SEQ ID NO:13 and shares 99.6% local similarity to the first 3582 polynucleotides of instant SEQ ID NO:13 (see attached sequence comparisons). Due to the high degree of homology between SEQ ID NO:6 and instant SEQ ID Nod 9, 10, and 13, one of skill in the art would recognize that complements of SEQ ID NO:6 would hybridize to instant SEQ ID NOs 9, 10, and 13. Bussemakers et al further teaches a method for determining a

predisposition for or the presence of prostate cancer in a patient comprising (a) contacting a biological sample of said patient with at least one oligonucleotide that hybridizes to a PCA3 polynucleotide selected from the group consisting of: (i) a polynucleotide according to SEQ ID NOs:9, 10, and 13; (ii) a polynucleotide sequence that hybridizes under high stringency conditions to the polynucleotide sequence in (i); and (iii) a polynucleotide sequence fully complementary to (i) or (ii); and contacting said biological sample with at least one oligonucleotide that hybridizes with a second prostate specific polynucleotide, (b) detecting in said biological sample an amount of PCA3 and second prostate specific polynucleotides; and comparing the amount of PCA3 polynucleotide that hybridizes to the oligonucleotide to a predetermined cut off value, and therefrom determining the presence or absence of prostate cancer in the biological sample (columns 24-25, in particular). Bussemakers further teaches a method wherein said second specific prostate specific nucleic acid is PSA (Example 2, in particular). Bussemakers further teaches a method wherein said PSA is a kallikrein family member. Further, without claiming any stringency of hybridization (see written description rejection), complements of SEQ ID NO:6 would hybridize to kallikrein. Bussemakers further teaches method wherein the amount of PCA3 polynucleotide and of the second specific prostate cancer polynucleotide is determined using an assay selected from the group consisting of: (a) an amplification assay and (b) a hybridization assay (column 37, in particular). Bussemakers further teaches method wherein said amplification assay is TMA (column 37, in particular). Bussemakers further teaches a method wherein said amplification of PCA3 and said prostate specific nucleic acid is

performed simultaneously (column 36, in particular). Bussemakers further teaches a method wherein said detection is performed by chemiluminescence (paragraph bridging columns 15-16, in particular). Bussemakers further teaches a method wherein said sample contains at least one prostate cell and said at least one cell is collected from said sample prior to step (a) (Example 2, in particular). Bussemakers further teaches a method wherein said nucleic acid is extracted from at least one prostate cell (column 37, in particular). Bussemakers further teaches a method wherein said nucleic acid is RNA (Example 2, in particular). Bussemakers further teaches a method wherein the sample is blood or prostate biopsy (see example 2). Bussemakers further teaches a method further comprising (c) repeating steps (a) and (b) using a biological sample from the patient at a subsequent point in time; and (d) comparing the relative amount of said PCA3 polynucleotide detected in step (c) to the relative amount of PCA3 polynucleotide detected in step (b) and therefrom monitoring the progression of prostate cancer in the patient (Example 2, in particular). Bussemakers further teaches a method wherein detection of the second prostate specific polynucleotide would provide some sort of validation to a negative result for PCA3 detection (Example 2, in particular). Bussemakers further teaches a method wherein RNA is extracted using a target capture method (Example 2, in particular). Bussemakers further teaches a method wherein said detection of PCA3 is carried out using chemiluminescent labels in a homogenous detection method (see paragraph bridging pages 15-16 and Example 2, in particular). Bussemakers further teaches a method for detecting prostate cancer in a human patient comprising (a) performing an in vitro nucleic acid amplification assay on a biological

sample of said patient or extract thereof using a first primer pair which is specific to a prostate cancer specific PCA3 sequence and a second primer pair which is specific to a prostate specific nucleic acid sequence; and (b) detection of said PCA3 nucleic acid sequence or a level thereof using chemiluminescence correlates with a risk of developing prostate cancer or to a presence of prostate cancer in said patient, and wherein an absence of detection of said PCA3 nucleic acid sequence or lower level thereof in said sample validates an absence of prostate cancer or a lower risk of developing same, when said second prostate specific nucleic acid is detected (see paragraph bridging pages 15-16 and Example 2, in particular). Bussemakers further teaches a method wherein said nucleic acid amplification is carried-out in real time (Example 2, in particular). Bussemakers further teaches a method wherein said amplification of PCA3 and said second prostate specific nucleic acid is performed simultaneously in one container (see column 36, in particular).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 10, 11, 15, 18-20, 22, 25, 26, 28, 29, and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bussemakers et al (US 7,008,765 B1; filed 4/9/98) in view of Baret (EP 0 256 932 A2; 2/24/88).

Claims 1-8, 10, 18-20, 22, 25, 26, 28, 29, and 37-40 are described above. Claims 11 and 15 are drawn to methods of chemiluminescent detection using acridinium ester compounds.

The teachings of Bussemakers et al are described above.

Baret teaches methods of chemiluminescent detection using acridinium ester compounds (page 4, in particular). Further, Baret teaches methods of chemiluminescent detection using acridinium ester compounds are particularly useful for nucleotide probe analysis because they provide very stable signals that are measurable for long periods of time (page 3, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use acridinium ester compounds as taught by Baret with chemiluminescent detection methods as taught by Bussemakers et al. Further, one would have been motivated to do so because Bussemakers et al. Further, one of skill in the art would have a reasonable expectation of success in performing the

claimed method since chemiluminescent detection using acridinium ester compounds is well known and conventional in the art.

Claims 1-8, 10, 12, 16, 18-20, 22, 23, 25, 26, 28, 29, and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bussemakers et al (US 7,008,765 B1; filed 4/9/98) in view of Schlegel et al (US 2002/0168638 A1; filed 1/24/01).

Claims 1-8, 10, 18-20, 22, 25, 26, 28, 29, and 37-40 are described above. Claims 12 and 16 are drawn to detection methods comprising using molecular beacons. Claims 22-23 are drawn to a method wherein the biological sample is urine.

The teachings of Bussemakers et al are described above.

Schlegel et al teaches methods of detecting prostate cancer comprising detecting PCA3 polynucleotides and PSA (paragraph 161, in particular). Schlegel et al further teaches methods of detecting markers of prostate cancer comprising using molecular beacons (paragraph 216, in particular). Schlegel et al further teaches that molecular beacons are useful for quantitating the presence of nucleic acids in a sample (paragraph 216, in particular). Schlegel et al further teaches methods wherein the biological sample is urine (paragraph 12 and 150, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use urine as the biological sample to as taught by Schlegel et al in the methods of detecting a predisposition for and the presence of prostate caner as taught by Bussemakers et al. Further, one would have been motivated to do so because urine is easily obtainable and that urine is a fluid which

contacts or passes through prostate cells or into which cells or proteins shed from prostate cells are capable of passing. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use molecular beacons as taught by Schlegel et al in the methods of detecting a predisposition for and the presence of prostate caner as taught by Bussemakers et al. Further, one would have been motivated to do so because molecular beacons are useful for quantitating the presence of nucleic acids in a sample. Further, one of skill in the art would have a reasonable expectation of success in performing the combined methods since urine analysis and molecular beacons are well known and conventional in the art.

Claims 1-8, 10, 18-20, 22, 24-26, 28, 29, and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bussemakers et al (US 7,008,765 B1; filed 4/9/98) in view of Schlegel et al (US 2002/0168638 A1; filed 1/24/01) and in further view of Goessl et al (Cancer Research, 11/1/00, 60:5941-5945).

Claims 1-8, 10, 18-20, 22, 25, 26, 28, 29, and 37-40 are described above.

The teachings of Bussemakers et al are described above. Claim 24 is drawn to a method wherein urine is collected following a digital rectal examination, thereby increasing the number of prostate cells in said sample.

Teachings of Schlegel et al are described above. Schlegel et al further teaches that urine is a fluid which contacts or passes through prostate cells or into which cells or proteins shed from prostate cells are capable of passing (paragraph 72 and 150, in particular). Schlegel et al further teaches a method wherein said urine is collected

following a digital rectal examination (paragraph 19, in particular). Schlegel et al further teaches detection of polynucleotide markers in patients that have had digital rectal exams (paragraph 110, in particular).

Goessl et al teaches a method of detecting prostate cancer markers in urine that has been collected following a digital rectal examination (page 5941, in particular). Goessl et al further teaches the routine method of digital rectal examination / prostate massage to enhance the amount of prostatic secretions in urine (page 5941 right column, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use urine following a digital rectal examination, as taught by Goessl et al, as the urine sample in the methods of detecting a predisposition for and the presence of prostate caner as taught by the combined teachings of Schlegel et al and Bussemakers et al. Further, one would have been motivated to do so because a digital rectal examination / prostate massage enhances the amount of prostatic secretions in urine (page 5941 right column of Goessl et al). Further, Schlegel et al teaches urine is easily obtainable and that urine is a fluid which contacts or passes through prostate cells or into which cells or proteins shed from prostate cells are capable of passing. Further, digital rectal examinations are routinely used to detect and monitor prostate cancer and combining methods of detection allows one to more accurately detect. Further, one of skill in the art would have a reasonable expectation of success in performing the combined methods since methods of analyzing

urine for molecular markers following digital rectal examinations are well known and conventional in the art.

Claims 1-8, 10, 18-22, 25, 26, 28, 29, and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bussemakers et al (US 7,008,765 B1; filed 4/9/98) in view of Cheung et al (Journal of Clinical Microbiology, 10/94, 2593-2597).

Claims 1-8, 10, 18-20, 22, 25, 26, 28, 29, and 37-40 are described above. Claim 21 is drawn to a method of extracting RNA using a silica-based method.

The teachings of Bussemakers et al are described above.

Cheung et al teaches a method of extracting RNA from a sample using a silica-based method (pages 2593-2594, in particular). Cheung et al further teaches that the silica-based method is at least as sensitive and in certain circumstances more sensitive than traditional phenol-chloroform extraction (page 2593, in particular). Cheung et al further teaches that this improved sensitivity may be due to more efficient recovery by silica particles (page 2593, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use silica particles as taught by Cheung et al in the methods of detecting a predisposition for and the presence of prostate caner by detecting RNA as taught by Bussemakers et al. Further, one would have been motivated to do so because silica-based methods of RNA purification are at least as sensitive and in certain circumstances more sensitive than traditional phenol-chloroform extraction. Further, one of skill in the art would have a reasonable expectation of

success in performing the combined methods because silica-based methods of RNA purification are well known and conventional in the art.

Claims 1-8, 10, 18-20, 22, 25-29, and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bussemakers et al (US 7,008,765 B1; filed 4/9/98) in view of Strickler et al (Cancer Epidemiology, Biomarkers & Prevention, 5/01, 10:523-533).

Claims 1-8, 10, 18-20, 22, 25, 26, 28, 29, and 37-40 are described above. Claim 27 is drawn to a method of spiking the biological sample with an internal control selected from the group consisting of purified nucleic acid, cells, viral particles containing target nucleic acids, and organelles.

The teachings of Bussemakers et al are described above.

Strickler et al teaches a method of spiking biological samples used for nucleic acid analysis with an internal control selected from the group consisting of purified nucleic acid, cells, viral particles containing target nucleic acids, and organelles (first paragraph on page 526 left column, in particular). Strickler et al teaches that said spiked samples are used as positive controls for PCR (page 530 right column and page 525 left column, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to spiked biological samples as taught by Strickler et al in the methods of detecting a predisposition for and the presence of prostate caner by detecting nucleic acids as taught by Bussemakers et al. Further, one would have been motivated to do so because spiked controls provide a positive control

for nucleic acid expression assays and roughly gage PCR sensitivity (page 525 left column, in particular). Further, one of skill in the art would have a reasonable expectation of success in performing the combined methods because methods of using spiked controls are well known and conventional in the art.

Summary

No claim is allowed. Claims 9, 13, 14, and 17 are rejected under 35 U.S.C. 112, first paragraph, but free of the prior art teaching methods comprising using nucleic acids with the SEQ ID NOs recited in the claims. The closest prior art for claims 9, 13, 14, and 17 is Bussemakers et al (US 7,008,765 B1; filed 4/9/98); however, this reference does not teach or suggest the specific sequences recited in claims 9, 13, 14, and 17.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

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